Final Summary Minutes
Advisory Committee for Reproductive Health Drugs meeting
September 8, 2008

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac

All external requests for the meeting transcripts and other materials should be submitted to the CDER, Freedom of Information office.

The Advisory Committee for Reproductive Health Drugs of the Center for Drug Evaluation and Research met on September 8, 2008 at the Hilton Washington DC/Rockville, Plaza Ballroom, 1750 Rockville Pike, Rockville, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a voting meeting. There were approximately two hundred (200) persons in attendance.

Issue: The committee discussed safety New Drug application (NDA) 22-242, FABLYN (lasofoxifene) 0.5 mg/day. The indication is the treatment of osteoporosis in post menopausal women at increased rick of fracture

Attendance:

Advisory Committee for Reproductive Health Drugs (Voting):
Sandra Carson, M.D., Chair, Daniel Gillen, Ph.D., Julia V. Johnson, M.D., James H. Liu, M.D.

Industry Representative Member Present (Non-Voting): Robert Gut, M.D., Ph.D.

Special Government Employee Consultants (Voting):
Eli Y. Adashi, M.D., Michael T. Collins, M.D., Jacqueline S. Gardner, Ph.D., Merrill Goozner *(Acting Consumer Representative)*, Diane Merritt, M.D., Lawrence M. Nelson, M.D., Natalie Compagni Portis (*Patient Representative)*, Clifford J. Rosen, M.D.; Bruce V. Stadel, M.D., MPH

FDA Participants (Non-Voting): Daniel Shames, M.D., Scott Monroe, M.D., Jerry Willett, M.D., Adrienne Rothstein, PharmD., Lisa Soule, M.D., Lisa Kammerman, Ph.D.

Designated Federal Official: Kalyani Bhatt, BS, MS

Open Public Hearing Speakers:
Cindy Pearson, National Women's Health,
Diana Zuckerman, National Research Center for Women & Families

AGENDA

Call to Order and Introductions	Sandra Carson, M.D., Chair Advisory Committee for Reproductive Health Drugs (ACRHD)
Conflict of Interest Statement	Kalyani Bhatt, B.S., M.S. Designated Federal Official, ACRHD
Welcome and Comments	Scott Monroe, M.D. Director, Division of Reproductive and Urologic Products (DRUP)
Sponsor Presentation	**Pfizer, Inc.**
Introduction	Brian A. Green, MS Director, Worldwide Regulatory Strategy and Development Pfizer Global Research and Development
Treatment of Osteoporosis: Unmet Medical Need and	Steven R. Cummings, MD Director, San Francisco Coordinating Center Professor Epidemiology & Biostatistics and Medicine, University of California at San Francisco
Lasofoxifene Program Overview and Efficacy	David D. Thompson, PhD Executive Director, Development Team Leader Pfizer Global Research and Development
Lasofoxifene Safety	Róisín Armstrong, PhD Senior Director, Clinical Lead Pfizer Global Research and Development
Lasofoxifene Risk Management	Claudia Turner, PhD Executive Director, Safety & Risk Management Pfizer Global Research and Development

Lasofoxifene Risk-Benefit

Steven R. Goldstein, MD
Professor of Obstetrics and Gynecology
New York University School of Medicine

FDA Presentation

Jerry Willett, M.D.
Medical Officer
Division of Reproductive and Urologic Products (DRUP)

Committee Questions to the Sponsor

Open Public Hearing

Committee Discussion of the Questions to the Committee

Adjournment

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Questions to the Committee

Introduction

In this Application, Pfizer, Inc. is seeking marketing approval for lasofoxifene tartrate tablets (0.5 mg per day) for the indication of "treatment of osteoporosis in postmenopausal women at increased risk of fracture." The Division of Reproductive and Urologic Products (DRUP) believes that the Applicant's pivotal Phase 3 clinical trial (Study 2181002, also referred as PEARL) has demonstrated that treatment with lasofoxifene for up to three years reduced the risk of a new or worsening radiographic vertebral fracture. Therefore, DRUP has no specific efficacy-related questions for the Committee. The following questions focus on safety issues and the overall assessment of the benefit/risk profile for lasofoxifene for the treatment of osteoporosis in postmenopausal women.

Question 1: All-Cause Mortality

Background: The hazard ratios for all-cause mortality in the lasofoxifene-treated subjects compared to subjects receiving placebo were increased in the PEARL study and the overall clinical Phase 2/3 development program as shown in the Table below. Unexpectedly, the hazard ratios were higher in the lower (0.25 mg) dose group.

	Lasofoxifene		Placebo
	0.25 mg	0.5 mg	
PEARL Study (5-year data)			
Subjects with event			
n	90	73	65
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%	3.2%	2.6%	2.3%
Hazard Ratio	1.38	1.12	
95% Confidence Interval	(1.00, 1.89)	(0.80, 1.56)	
Overall Phase 2/3 Program			
Subjects with event			
n	94	76	65
%	2.1%	1.8%	1.4%
Hazard Ratio	1.44	1.16	
95% Confidence Interval	(1.05, 1.97)	(0.84, 1.62)	

For the PEARL study, the excess mortality in the lasofoxifene treatment groups was observed primarily in the Applicant's adjudicated categories of cancer (i.e., brain, lung, and gastrointestinal), stroke, and other vascular (i.e., pulmonary embolus).

Question 1a. **[Vote]** Do you believe that these data regarding all-cause mortality reflect a true increase in mortality in lasofoxifene-treated subjects? Please answer with "yes," "no," or "unable to determine" and provide the rationale for your assessment.

Yes – 2 *No - 4* *Unable to Determine - 7*

The Committee expressed concern about the lack of a dose-response relationship, and, for the most part, felt that there was not sufficient data to make a decision on mortality.

Question 1b. [Discussion only] If you believe there is a true increase in mortality, do you believe that the Applicant's regional analysis of the distribution of the deaths, which shows the imbalance to be largely in Region 2 (i.e., Mexico, Central, and South America), is reassuring regarding the safe use of lasofoxifene by women in the U.S.?

The Committee Members who voted "yes" to Question 1a felt that the data from the 0.25 mg dose, in particular, did show a true increase in mortality, and that the date from the 0.5 dose could not be discounted. They were concerned by the disparity in the data between Region 2 and the rest of the data, and felt that the diversity of the United States population made it important to continue to consider the data from Region 2.

Question 2: Venous Thromboembolic Events [Vote]

Are the safety findings for venous thromboembolic events in lasofoxifene-treated women of greater concern than those associated with the use of approved hormonal products for postmenopausal osteoporosis or menopausal symptom therapy?

Yes – 2 *No - 9* *Unable to Determine - 2*

In general, the Committee felt that the risk for venous thrombolic events was similar to that found with the other SERMS, but recommends long-term follow-up to determine the risk with use over a larger number of years. More data from extended studies will provide information on the most practical way to reduce long-term risk.

Question 3: Gynecological Issues

Question 3a. **[Discussion only]** Do the gynecologic adverse events associated with lasofoxifene treatment (e.g., endometrial thickening and vaginal bleeding) entail a significant management problem for general healthcare providers and/or burden for patients?

Question 3b. **[Discussion only]** Should endometrial biopsies be performed in women taking lasofoxifene who are not having vaginal bleeding, but are found incidentally to have endometrial thickening on an imaging procedure?

Question 3a and 3 b were discussed simultaneously:

The Committee relayed that uterine scans are not usually performed unless there are symptoms or complaints, so the endometrial thickening in the absence of vaginal bleeding is unlikely to be discovered in many cases.

The Committee discussed the effect of the medication on gynecologic adverse events and encouraged ongoing study of these effects. The standards for endometrial biopsy for this medication should be similar to the current recommendation for other medications in this class (endometrial biopsy when there is vaginal bleeding).

Question 4: Benefit/Risk Profile

Question 4a. [Vote] Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with lasofoxifene is likely to outweigh the risks?

If so, would this population be:

(1) all women with postmenopausal osteoporosis,

(2) limited to a subgroup at a higher risk for fracture than the general population of women with osteoporosis, or

(3) limited to women who do not tolerate other osteoporosis therapies or in whom other osteoporosis therapies are not appropriate?

Yes-9 *No-3* *Abstain -1*

In general, the Committee felt that lasofoxifene treatment should be limited to women with osteoporosis, with a high risk for fracture, with some Committee Members also limiting it to those who are unable to take other osteoporosis medications, in particular, the bisphosphonates. More information is needed to better identify those with the best benefit/risk ratio, and discussions with the patient about their personal benefit/risk ratio should be encouraged.

Question 4b. If you believe that treatment should be limited to a "higher risk for fracture" population, how would you define this population?

High risk of fracture could be identifed as 20% for vertebral fractures and 10% risk for hip fracture.

Ideally, the label would reflect the limitations of the current data (no head-to-head study with other osteoporosis therapies, no data from very long term studies) so that the practicing clinician can better counsel the osteoporosis patient at high risk of fracture.

The meeting adjourned at approximately 3:00 PM

I certify that I attended the September 8, 2008meeting of the Advisory Committee for Reproductive Health Drugs and that these minutes accurately reflect what transpired.

_____/s/_____
Kalyani Bhatt
Designated Federal Official
ACRHD

_____/s/_____
Sandra Carson, M.D.
Chair, ACRHD